



PATENT
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CLIENT REFERENCE NO. CHOP-0004-DF

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: High *et al.*
Serial No.: 09/393,844
Filed: September 10, 1999
Title: METHODS AND COMPOSITIONS FOR USE IN GENE THERAPY FOR
TREATMENT OF HEMOPHILIA

Art Unit: 1636
Examiner: Gansheroff, L.

Assistant Commissioner for Patents
Washington, DC 20231

DECLARATION UNDER 37 C.F.R. §1.131

Dear Sirs:

I, Dr. Katherine High, do hereby declare and state that:

1. I am a co-inventor of the subject matter described and claimed in United States Patent Application Serial No. 09/393,844, filed September 10, 1999, entitled: "METHODS AND COMPOSITIONS FOR USE IN GENE THERAPY FOR TREATMENT OF HEMOPHILIA".
2. I am familiar with the prosecution history of Application Serial No. 09/038,910.
3. I understand that the Examiner has cited Wiener *et al.* (WO96/15777) under 35 U.S.C. §102(a), Wilson *et al.* (U.S. Patent No. 5,866,552) under 35 U.S.C. §102(e), Skulimowski *et al.* (Methods in Molecular Genetics 7:3 (1995)) under 35 U.S.C. §103(a) and Thiell *et al.* (U.S. Patent No. 5,817,784) under 35 U.S.C. §103(a) against the claims of Application Serial No. 09/393,844.

4. I submit that Wiener *et al.*, Wilson *et al.*, Skulimowski *et al.* and Thiehl *et al.* are not available as prior art under 35 U.S.C. §§102 or 103.
5. Prior to the publication date of Wiener *et al.*, Wilson *et al.*, Skulimowski *et al.* and Thiehl *et al.* the recombinant AAV vector including DNA encoding Factor IX was first constructed by me or under my direction at the Children's Hospital of Philadelphia, Philadelphia, Pennsylvania. We were diligent from the time that we first discussed and conceived the invention with respect to the Factor IX AAV vector, reduced to practice the Factor IX AAV vector, and up until the time of filing the patent application.
6. Evidence of the conception and reduction to practice of the present invention is supplied in the form of a copy of a page from our laboratory notebooks (Exhibit 2), prior to October 3, 1995, the publication date of Skulimowski *et al.*, the earliest published reference of Wiener *et al.*, Wilson *et al.*, Skulimowski *et al.* and Thiehl *et al.* This page shows our reduction to practice of the recombinant AAV vector including DNA encoding Factor IX.
7. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date:

5/23/01

Katherine A. High
Katherine A. High, Ph.D. M.D.

PLEP-FR ultra

10x

SacI

H₂O

30ul

5ul

5ul

10ul

pAd-Bgl II

10x

Bgl II

H₂O

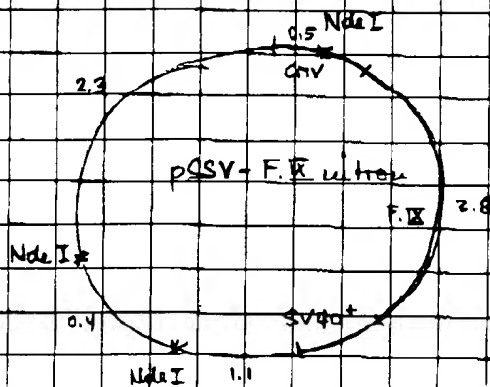
5ul

3ul

3ul

19ul

- made 3.2% sodium-citrate solution to anti-coagulate mouse blood (1.6g sodium citrate / 50 ml)



- | | | | |
|---|--------|---|--------|
| ① | 0.4 kb | ② | 0.4 kb |
| | 2.8 kb | | 1.6 kb |
| | 4.9 kb | | 6.1 kb |

+ HeLa's

- 293 cells in 96-well plate: 100ul 101K Ad-lacZ (volume 50ul) (1930)

- ④ Ad-lacZ 1.5×10^{12} part / ml (1.5×10^9 part / ml)

- | | | | | |
|---|-------------------|---|-------------|----------------------|
| ① | 200ul DMEM 2% FBS | + | 3ul Ad-lacZ | |
| ② | 150ul 75ul -v- | + | 50ul ① | $\hat{=}$ (1/4 of ①) |
| ③ | 150ul 75ul -v- | + | 50ul ② | |

- ⑤ Ad-lacZ 1.5×10^{10} part / ml (1.5×10^7 part / ml)

- | | | | | |
|---|-------------------|---|--------------|----------------------|
| ① | 180ul DMEM 2% FBS | + | 20ul Ad-lacZ | |
| ② | 70ul -v- | + | 70ul ① | $\hat{=}$ (1/2 of ①) |
| ③ | 70ul -v- | + | 70ul ② | |